Study Title: OPtimal Treatment by Invoking biologic Clusters in Renal Cell Carcinoma (OPTIC RCC)
Version Date: 06SEPT2023

Part 1 of 2: MASTER CONSENT NCT05361720

Name of participant: _____ Age: _____

You are being invited to take part in a research study. This study is a multi-site study, meaning it will take place at several different locations. Because this is a multi-site study this consent form includes two parts. Part 1 of this consent form is the Master Consent and includes information that applies to all study sites. Part 2 of the consent form is the Study Site Information and includes information specific to the study site where you are being asked to enroll. Both parts together are the legal consent form and must be provided to you.

Key Information:
The first section of this document contains some key points that the research team thought you would find important. The study is described in more detail after this section. If you do not understand something, please ask someone.

Key information about this study:
You are being asked to take part in this research study because you have been diagnosed with advanced kidney cancer. This study is being done to address the following question:

- Can genetic testing of tumor tissue help predict the treatment regimen to which kidney cancer is most likely to respond?

We are doing this study because currently there are two categories of treatment regimens for advanced kidney cancer:

- One treatment includes two immunotherapy drugs (one drug called nivolumab, in combination with a second drug called ipilimumab), administered as separate intravenous (IV) infusions into a vein.
- The other treatment includes an immunotherapy drug (nivolumab) given by intravenous infusion into a vein, in combination with a second drug (called cabozantinib), administered as oral pills taken by mouth.

Both of the above treatment regimens (nivolumab +ipilimumab and nivolumab +cabozantinib) are considered standard-of-care and are FDA-approved for the treatment of advanced kidney cancer.

Currently however, it is unknown which of these two approved treatment options is more likely to work against your kidney cancer.

In this study, it is hoped that by testing the makeup (genes) of your tumor, we can help match a treatment (from one of the above two treatment options) to your specific cancer and increase the chance that your disease will respond to treatment.

The treatment you receive in this study will be determined by genetic testing of your tum or tissue. Genetic testing (called RNA-sequencing) will be performed on your tumor tissue, in order to determine the group of genes (referred to as the genetic "cluster") detected in and associated with your tumor type.

There are two treatment groups in this study:

- Patients with genetic Cluster 1 or 2 will receive nivolumab and cabozantinib.
- Patients with genetic Cluster 4, or 5 will receive nivolumab and ipilimumab.

Detailed Information:

The rest of this document includes detailed information about this study (in addition to the information listed above).

The purpose of this study is to learn if genetic testing of tumor tissue can help doctors select the optimal treatment regimen to which advanced kidney cancer is more likely to respond.

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services, or other rights. You can stop being in this study at any time. If we learn something new that may significantly affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study. Your medical record will contain a note saying you are in a research study and may contain some research information about you. Anyone you authorize to receive your medical record will also get this information.

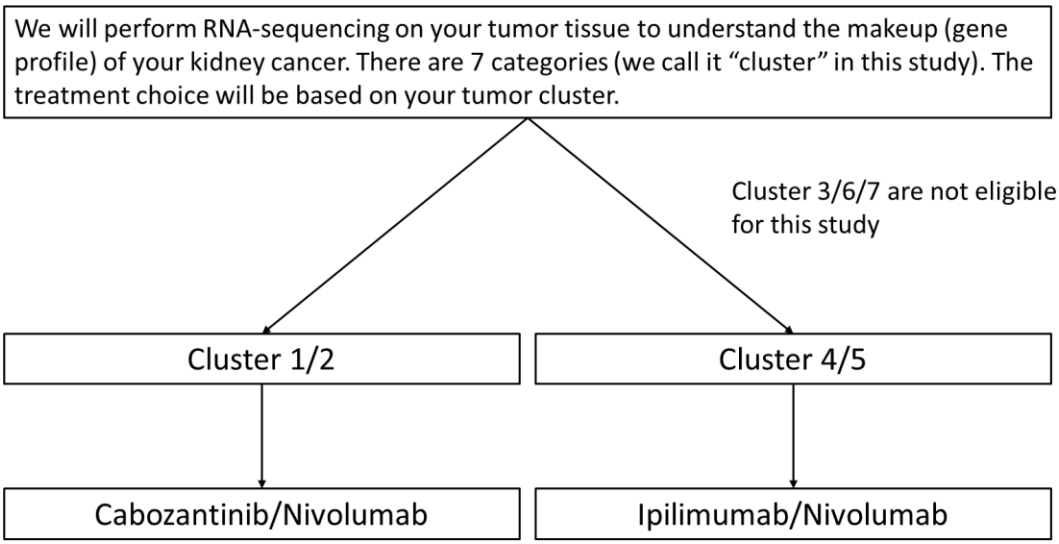
If you choose to not participate in this study, your oncologist will likely recommend one of the above treatment options, as they are all FDA-approved therapies for advanced kidney cancer.

As mentioned above, the current FDA-approved regimens for advanced kidney cancer fall into two categories. One treatment combination includes two immunotherapy drugs (nivolumab plus ipilimumab), which are delivered by separate intravenous infusions into a vein. The other combination is one immunotherapy drug (nivolumab infusion) plus an oral pill taken by mouth (cabozantinib).

Nivolumab and ipilimumab are "immunotherapies" which release the brakes of the immune system, thus allowing your own immune system to better kill cancer cells. Cabozantinib is a "targeted therapy" specifically designed to block certain biological mechanisms needed for growth of cancer cells. In kidney

cancer, cabozantinib blocks a tumor's blood supply.

In this study, your tumor tissue (either from a previous surgery/biopsy, or from a new biopsy) will be genetically tested by a technique called RNA-sequencing to determine the makeup of genes detected in your tumor. As shown in the diagram below, we will categorize your cancer into one of 7 categories (called "clusters"):



Based on tumor cluster (determined by genetic testing of tumor tissue), each patient in this study will be treated with either nivolumab plus cabozantinib, or nivolumab plus ipilimumab:

- If your tumor belongs to cluster 1or 2 (about 42% of kidney cancer), you will be treated with nivolumab and cabozantinib.
- If your tumor belongs to clusters4or 5 (about 26% of kidney cancer), you will be treated with nivolumab and ipilimumab.
- If your tumor belongs to cluster 3, 6or 7 (about 32% of kidney cancer), you will not be enrolled on this study, and your doctor will discuss therapy options.

Your responsibilities during this study include:

- Keeping your study appointments.
- Telling your study doctor about:
  - all medications and supplements you are taking
  - any side effects
  - any doctors' visits or hospital stays outside of this study
  - if you have been or are currently in another research study.

Side effects and risks that you can expect if you take part in this study:
There are no investigational drugs used for treatment of your disease in this study. All treatment regimens you will receive in this study for advanced kidney cancer are FDA-approved. You will be monitored for side effects and response to treatment as would normally be done for patients outside of clinical trials.

Radiation Risk
This research study may involve exposure to radiation from up to 1 CT scan of the Chest, Abdomen and Pelvis and 1 Whole Body Bone Scan. This radiation exposure is not necessary for your medical care and is for research purposes only. The total amount of radiation that you may receive by participating in this study is equal to your body receiving 56 months (4.7 years) of radiation from your natural surroundings, or about 28% of the amount allowed in a year for people who are exposed to radiation as part of their work. If you stay in the study past the first year you may have some more procedures which expose you to radiation. You should talk to the study doctor or nurse if you have questions about radiation exposure.

Risks of Blood Collection
In this study, additional blood samples (about 2-3 tablespoons) for research purposes will be collected at four time points: before treatment initiation, at Cycle 2 and Cycle 4 after treatment initiation, and at the end of treatment. You may feel bothered or pained from the needlestick. You may have a bruise or the blood draw site may get infected. It is rare, but some people faint. These blood samples are intended to be drawn at the same time as standard-of-care laboratory testing associated with your treatment.

Risks that are not known:
All treatment regimens you will receive in this study for advanced kidney cancer are FDA-approved. However, it is possible there may be risks that we do not know about at this time.

Other Risks:
You are being asked to give tumor tissue and blood samples for this study. What we learn about you from these samples will be used for research and to determine your study eligibility and the treatment for kidney cancer that you receive in this study.

The purpose of this study is to use the genetic makeup (genes) detected in samples of your tumor, in order to determine the best treatment regimen for your disease. There will be a waiting period during collection and testing of your tumor sample(s) before knowing the genetic cluster of your tumor type. We estimate this to be about 2 to 4 weeks. Thus, one risk of participating in this study is that the start of your therapy could be delayed.

Genes are the instruction manual for your body. The genes you get from your parents decide what you look like and how your body behaves. They can also tell us a person's risk for certain diseases and how they may respond to treatment. In this study, we are mainly looking into the genetic changes in your tumor (in other words, changes that are not inheritable or able to pass to your children or offspring). However, there is a very small chance we might find inheritable genetic changes.

One risk of giving samples for this study may be the release of your name that could link you to the stored samples and/or the results of the tests run on your samples. This may cause problems with insurance or getting a job.

To help prevent this, these samples will be given a code. Only the study staff will know the code. The name that belongs to the code will be kept in a locked file or in a computer with a password. Only the physician and study team will have access to your name.

Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums. Employers with 15 or more employees may not use your genetic information that comes from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Your sample will be used to make DNA and/or RNA that will be kept for an unknown length of time (maybe years) for future research. The sample will be destroyed when it is no longer needed.

Good effects that might result from this study:

a) The benefits to science and humankind that might result from this study:
Participating in this study may help patients with cancer get better care in the future.

b) The benefits you might get from being in this study:
Based on your tumor cluster, you may receive the systemic regimen for which your cancer is more likely to respond. Whether getting a specific treatment based on your cluster leads to a better response is not known, however.

Procedures to be followed:

We will collect blood samples (about 3-4 tablespoons) at four time points: before treatment initiation, at Cycle 2 and Cycle 4 after treatment initiation, and at the end of treatment for research purposes.

Otherwise, no extra visits or scans are anticipated during this study, which you would not otherwise typically receive during standard treatment for your disease outside of this clinical trial. Saliva sample will be collected prior to starting treatment for genetic research.

What we learn about you from this sample will not be put in your health record. Your test results will not be shared with you or your doctor. No one else (like a relative, boss, or insurance company) will be given your test results.

Reasons why the study doctor may take you out of this study:

Your study doctor might take you out of the study for reasons such as:

- You are unable to tolerate the treatment, or you have a side effect and the study doctor feels should end the treatment.
- Your disease spreads or gets worse (progresses).
- You have another serious illness or need major surgery.

- You do not follow the study doctor's instructions.
- Your health changes or new information becomes available and the study doctor feels it is no longer in your best interest for you to continue in the study, or decides to stop the study.

If you are removed from the study, the reason will be explained to you.

What will happen if you decide to stop being in this study?
If you decide to stop being part of the study, you should tell your study doctor. Deciding to not be part of the study will not change your regular medical care in any way.

If you decide to not participate in this study, your doctor will discuss other options, such as:

- You may choose to have the usual treatment for kidney cancer described above on page one outside of a clinical trial.
- You may choose to take part in a different research study, if one is available.
- You may choose not to be treated for cancer.
- You may choose to only get comfort care to help relieve your symptoms and not get treated for your cancer.

Clinical Trials Registry.
A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this Web site at any time.

Disclosure:
The Department of Defense (DoD) is providing support for this study. The Department of Defense will have access to research records as part of its human subjects' protection oversight activities.

Privacy:
Any samples and information about you may be made available to others to use for research. To protect your privacy, we will not release your name. You will not receive any benefit as a result of the tests done on your samples. These tests may help us or other researchers learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Your samples may be used to make new products or tests. These may have value and may be developed and owned by the study staff, Vanderbilt University, Vanderbilt University Medical Center, and/or others. If this happens, there are no plans to provide money to you.

You will get a copy of this form after it is signed.

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Please check Yes or No to the questions below, regarding your decisions about participation in the required and optional parts of this study:

I agree that my blood/tissue/fluid samples and related health information may be used for current research in this study related to kidney cancer:

☐ Yes ☐ No

I agree that my blood/tissue/fluid samples and related health information may be kept in a biobank and stored/shared for future cancer research:

☐ Yes ☐ No

I agree that my blood/tissue/fluid samples and related health information may be kept in a biobank for use in future health research in other health problems (such as arthritis, heart disease, etc):

☐ Yes ☐ No

I agree that my study doctor, or someone on the study team, may contact me or my doctor to see if I wish to participate in other research in the future:

☐ Yes ☐ No

Signature: _____ Date: _____

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Study Results:
The people who may request, receive or use your private health information include Vanderbilt University Medical Center and its agents or contractors, study safety monitors and auditors, data managers and other agents and contractors used by the study team, researchers and study team members. Additionally, we may share your information with other people at Vanderbilt, for example if needed for your clinical care or study oversight. Also, your records may be seen by people from regulatory authorities (such as the U.S. Food and Drug Administration [FDA]), auditors, and the Institutional Review Board [IRB]). By signing this form, you give permission to the research team to share your information with others outside of Vanderbilt University Medical Center. This may include any funders, (DoD), of the study and their agents or contractors, outside providers, study safety monitors, government agencies, and other sites in the study. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

Institutional Review Board
Informed Consent Document for Research
STUDY SITE INFORMATION

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Part 2 of 2: STUDY SITE INFORMATION

Site Name:	Vanderbilt University Medical Center
Site Principal Investigator:	Dr. Brian Rini, MD, FASCO
Site Principal Investigator Contact:	[redacted]

This part of the consent form includes information about the site that is asking you to participate in this study and is specific to participation at your site only. Before making your decision, both the site-specific information and the general study information should be reviewed with you. Your medical record will contain a note saying you are in a research study and may contain some research information about you. Any one you authorize to receive your medical record will also get this information.

Site specific procedures and risks:
The purpose of this study is to learn if genetic testing of tumor tissue can help doctors select the optimal treatment regimen to which advanced kidney cancer is more likely to respond. About 54 total patients are anticipated to enroll in this study at Vanderbilt University Medical Center and possibly additional academic medical centers in the United States.

Side effects and risks that you can expect if you take part in this study:
There are no investigational drugs used for treatment of your disease in this study. All treatment regimens you will receive in this study for advanced kidney cancer are FDA-approved. You will be monitored for side effects and response to treatment as would normally be done for patients outside of clinical trials.

Payments for your time spent taking part in this study or expenses:
You will not be paid for your participation in this study.

Costs to you if you take part in this study:
If you agree to take part in this research study, you and/or your insurance will not have to pay for the tests and treatments that are being done only for research. However, you are still responsible for paying for the usual care you would normally receive for the treatment of your illness. This includes treatments and tests you would need even if you were not in this study. These costs will be billed to you and/or your insurance.

You have the right to ask what it may cost you to take part in this study. If you would like assistance, financial counseling is available through the Vanderbilt Financial Assistance Program. The study staff can help you contact this program. You have the right to contact your insurance company to discuss the costs of your routine care (non-research) further before choosing to be in the study. You may choose not to be in this study if your insurance does not pay for your routine care (non-research) costs and your doctor will discuss other treatment plans with you.

Payment in case you are injured because of this research study:
If it is determined by Vanderbilt and the Investigator that an injury occurred, then you and/ or your insurance may be billed for the cost of medical care provided at Vanderbilt to treat the injury. You will be responsible for any copayments or deductibles associated with the treatment of that injury.

There are no plans for Vanderbilt to pay for the costs of any additional care. There are no plans for Vanderbilt to give you money for the injury.

Who to call for any questions or in case you are injured:
If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact Dr. Brian Rini at [redacted]. If you cannot reach the research staff, please page the study doctor at [redacted].

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the Vanderbilt University Medical Center Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

Additional information about your local site:

Clinical Trials Reporting Program.
Vanderbilt's NCI-Designated Cancer Center or the Sponsor registers National Cancer Institute (NCI)-supported clinical trials with NCI though their Clinical Trials Reporting Program (CTRP) to provide study related information. The data provided will include the following identifiable information that may identify you: birth month/year and five-digit zip code. NCI uses the data to manage and enhance the nation's investment in cancer research.

Confidentiality:
All efforts within reason will be made to keep your personal information in your research record confidential but total confidentiality cannot be guaranteed. Your information and samples will be given a code. Dr. Rini, his staff, and other authorized people will be the only people who know your personal information.

Study data will be recorded in a Vanderbilt electronic database which is maintained by a research coordinator and data manager at Vanderbilt. The electronic database is password protected in order to help protect your identity. Your study records will be locked up in the clinical trials office. Vanderbilt may share your information, without identifiers, to others or use it for other research projects not listed in this form. Vanderbilt, Dr. Rini and his staff will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use or transfer of this de-identified information.

The Department of Defense (DoD) is providing support for this study. The Department of Defense will have access to research records as part of its human subjects' protection oversight activities.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

Authorization to Use/Disclose Protected Health Information
What information is being collected, used, or shared?

To do this research, we will need to collect, use, and share your private health information. By signing this document, you agree that your health care providers (including both Vanderbilt University Medical Center and others) may release your private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

Who will see, use or share the information?

The people who may request, receive or use your private health information include Vanderbilt University Medical Center and its agents or contractors, study safety monitors and auditors, data managers and other agents and contractors used by the study team, researchers and study team members. Additionally, we may share your information with other people at Vanderbilt, for example if needed for your clinical care or study oversight. Also, your records may be seen by people from regulatory authorities (such as the U.S. Food and Drug Administration [FDA]), auditors, and the Institutional Review Board [IRB]). By signing this form, you give permission to the research team to share your information with others outside of Vanderbilt University Medical Center. This may include any funders, (DoD), of the study and their agents or contractors, outside providers, study safety monitors, government agencies, and other sites in the study. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

Do you have to sign this Authorization?
You do not have to sign this Authorization, but if you do not, you may not join the study.

How long will your information be used or shared?
Your Authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

_____ _____
Date Signature of patient/volunteer

Consent obtained by:

_____ _____
Date Signature

_____
Printed Name and Title

Time: _____